

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022377Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

BIOPHARMACEUTICS REVIEW

NDA# 22375
Drug Sumatriptan Succinate
Formulation Auto-Injector
Type Original NDA
Sponsor King Pharmaceuticals
Letter Date July 16th 2008
Reviewer/Team Leader Patrick Marroum, Ph.D.

Background:

King Pharmaceuticals is submitting this application to seek approval of a new pre-filled fully assembled single use auto injector product containing 6 mg of sumatriptan succinate salt delivered in a 0.5 ml subcutaneous dose. The product is intended for the acute treatment of migraine attacks with or without aura and the acute treatment of cluster headache episodes.

The basis for reference for the safety and efficacy of this application under Section 505(b)(2) of the Act is GlaxoSmithKline NDA20-080 for Imitrex auto injector also known as the ImitrexSTATdose System. While both these 2 products are autoinjector Systems intended for either self or caregiver administration, the systems differ significantly with respect to design and operating principle. The proposed product in this submission is pre-filled, fully assembled and ready-for-use while the Imitrex system requires preparatory assembly of pre-filled cartridges with the STATdose injector system prior to use. The sponsor is requesting an in vivo bioequivalence bioavailability waiver based on the fact that the compositions of the 2 products are identical both in terms of active drug and inactive excipients. The table below shows the compositional formula which is identical to the approved Imitrex STATdose

Table 3. Sumatriptan Succinate Formulation

Ingredient	8.4 mg/0.5 mL ¹ (Equivalent to 6 mg/0.5 mL as Sumatriptan Base)	
	Amount per mL	Amount per 0.5 mL
Sumatriptan Succinate	16.8 mg (equivalent to 12 mg as sumatriptan base)	8.4 mg (equivalent to 6 mg as sumatriptan base)
Sodium Chloride USP	7.0 mg	3.5 mg
Water for Injection USP	(b) (4)	(b) (4)
		(b) (4)

COMMENTS:

According to the CFR 320.22 (b)

For certain drug products, the in vivo bioavailability or bioequivalence of the drug product may be self-evident. FDA shall waive the requirement for the submission of evidence obtained in vivo measuring the bioavailability or demonstrating the bioequivalence of these drug products. A drug product's in vivo bioavailability or bioequivalence may be considered self-evident based on other data in the application if the product meets one of the following criteria:

(1) The drug product:

(i) Is a parenteral solution intended solely for administration by injection, or an ophthalmic or otic solution; and

(ii) Contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application or abbreviated new drug application.

This sumatriptan succinate, product is a parenteral solution intended for subcutaneous injection that contains the same active and inactive ingredients in the same concentration as a drug product that is subject of an approved NDA.

However, since these two auto injectors are different with respect to design and operating principles, the amount of drug as well as the site of injection can be different between the 2 systems potentially leading to different absorption profile of the drug from the subcutaneous site of injection

RECOMMENDATION

The Office of New Drug Quality Assessment has reviewed this submission and recommends granting an in vivo bioavailability/bioequivalence waiver since the submitted in vitro data showed that the delivery of the drug from the two auto-injectors are similar (Imitrex STATdose and the sumatriptan (b) (4))

Patrick Marroum, Ph. D.
Office of New Drug Quality Assessment

Date_____

cc: Heiman, claffey, Henry

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/s/

Patrick Marroum
5/8/2009 09:54:50 AM
BIOPHARMACEUTICS

BIOPHARMACEUTICS REVIEW

NDA# 22375
Drug Sumatriptan Succinate
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Type Original NDA
Sponsor King Pharmaceuticals
Letter Date July 16th 2008
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The basis for reference for the safety and efficacy of this application under Section 505(b)(2) of the Act is GlaxoSmithKline NDA20-080 for Imitrex auto injector also known as the ImitrexSTATdose System. While both these 2 products are autoinjector Systems intended for either self or caregiver administration, the systems differ significantly with respect to design and operating principle. The proposed product in this submission is pre-filled, fully assembled and ready-for-use while the Imitrex system requires preparatory assembly of pre-filled cartridges with the STATdose injector system prior to use. The sponsor is requesting an in vivo bioequivalence bioavailability waiver based on the fact that the compositions of the 2 products are identical both in terms of active drug and inactive excipients. The table below shows the compositional formula which is identical to the approved Imitrex STATdose

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However, since these two auto injectors are different with respect to design and operating principles, the amount of drug as well as the site of injection can be different between the 2 systems potentially leading to different absorption profile of the drug from the subcutaneous site of injection

RECOMMENDATION

The Office of New Drug Quality Assessment has reviewed this submission and recommends granting an in vivo bioavailability/bioequivalence waiver only if the sponsor submitted in vitro data showing that the delivery of the drug from the two auto-injectors are similar (Imitrex STATdose and the sumatriptan ^{(b)(4)} In the event that such data are unavailable or the results show that the drug delivery is different between the 2 autoinjectors then a bioequivalence study would be needed.

Date_____

Patrick Marroum, Ph. D.
Office of New Drug Quality Assessment

cc: Heiman, claffey, Henry

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/s/

Patrick Marroum
4/15/2009 02:56:23 PM
BIOPHARMACEUTICS

Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name):	Sumatriptan Succinate
NDA:	22-377
SUBMISSION DATE	07/16/2008
PRODUCT (Brand Name):	(b)(4)™
DOSAGE FORM:	Autoinjector
DOSAGE STRENGTH:	12 mg/mL
INDICATION:	Acute treatment of migraine attacks with or without aura and the acute treatment of cluster headache episodes.
NDA TYPE:	505 (b)(2)
SPONSOR:	King Pharmaceuticals Inc.
REVIEWER:	Jagan Mohan Parepally, Ph.D.
TEAM LEADER:	Veneeta Tandon, Ph.D.
OCP DIVISION:	DCP 1
OND DIVISION:	HFD 120

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I. EXECUTIVE SUMMARY

(b) (4) (Sumatriptan Succinate) autoinjector is a pre-filled, fully assembled single-use disposable auto-injector product containing 6 mg of sumatriptan (base) as the succinate salt delivered in a 0.5 mL subcutaneous dose. This product is intended for the acute treatment of migraine attacks with or without aura and the acute treatment of cluster headache episodes.

Imitrex STATdose System (NDA 20-080) is the reference product and these systems differ with respect to design and operating principle. The proposed drug product is prefilled, fully-assembled and ready-for-use, while the Imitrex STATdose System requires preparatory assembly of pre-filled cartridges with the STATdose injector system prior to use. The formulation used in (b) (4)™ is similar to formulation in the STATdose system.

The present submission contains a single usability study to provide the instructional use information in the labeling for the proposed (b) (4)™. The Phase III clinical study (K644-07-3001) was conducted to assess the use of this drug delivery system for self-administration of subcutaneous sumatriptan succinate by patients experiencing migraine attacks. In addition, the sponsor relies on safety and efficacy information in label of the reference Imitrex STATdose system to support the approval of the proposed (b) (4)™ Autoinjector.

The sponsor has requested a waiver for an in vivo bioequivalence study comparing (b) (4)™ Auto-Injector to reference Imitrex STATdose system. Bio-waiver request for this application will be reviewed by ONDQA.

Recommendation

There were no new clinical pharmacology studies to review in this NDA. Labeling recommendations outlined in the Detailed Labeling Recommendations section of the review (page 5-33) should be conveyed to the sponsor.

Phase IV Commitments

None.

Jagan Mohan Parepally, Ph.D.
Reviewer
Division of Clinical Pharmacology 1

Date

Veneeta Tandon, Ph.D.
Team Leader
Division of Clinical Pharmacology 1

Date

cc: HFD-120 NDA 22-377
 HFD-860 Mehul Mehta, Ramana Uppoor, Veneeta Tandon, Jagan Parepally

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/s/

Jagan Parepally
4/8/2009 06:32:37 AM
PHARMACOLOGIST

Veneeta Tandon
4/8/2009 06:51:39 AM
BIOPHARMACEUTICS

31 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this
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Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	22-377	Brand Name	(b) (4)™
OCPB Division (I, II, III)	DCP-1	Generic Name	Sumatriptan Succinate
Medical Division	HFD-120	Drug Class	5-HT Agonist
OCPB Reviewer	Jagan Mohan Parepally	Indication(s)	Treatment of Migraine
OCPB Team Leader (Acting)	Ta-Chen Wu	Dosage Form	Auto-injector
Date of Submission	07/16/2008	Dosing Regimen	6 mg x 2 in 24 hrs
Estimated Due Date of OCPB Review	3/29/2009	Route of Administration	Subcutaneous Injection
PDUFA Due Date	5/17/2009	Sponsor	King Pharmaceuticals, Inc.
Division Due Date	4/15/2009	Priority Classification	S

Clin. Pharm. and Biopharm. Information

Summary: This is a 505(b)(2) NDA (paper submission) to support the marketing approval of (b) (4) (Sumatriptan Succinate) autoinjector, which is a new pre-filled, fully assembled single-use disposable auto-injector product containing 6 mg of sumatriptan (base) as the succinate salt delivered in a 0.5 mL subcutaneous dose. This product is intended for the acute treatment of migraine attacks with or without aura and the acute treatment of cluster headache episodes.

Imitrex STATdose System (NDA 20-080) is the reference product and these systems differ with respect to design and operating principle. The proposed drug product is pre-filled, fully-assembled and ready-for-use, while the Imitrex STATdose System requires preparatory assembly of pre-filled cartridges with the STATdose injector system prior to use. The formulation used in (b) (4)™ is similar to formulation in the STATdose system.

The present submission contains a single usability study to provide the instructional use information in the labeling for the proposed (b) (4)™. This is a Phase III clinical study (K644-07-3001) conducted to assess the use of this drug delivery system for self-administration of subcutaneous sumatriptan succinate by patients experiencing migraine attacks. In addition, the sponsor relies on safety and efficacy information in label of the reference imitrex STATdose system to support the approval of the proposed (b) (4)™ Autoinjector.

The sponsor requests a waiver for an in vivo bioequivalence study comparing (b) (4)™ Auto-Injector to reference Imitrex STATdose system.

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			

Labeling	X	1		K644-07-3001 Phase 3 Clinical (usability) study Objective: Assessment of self injection
Reference Bioanalytical and Analytical Methods	-			
I. Clinical Pharmacology				
Mass balance:	-	-	-	
Isozyme characterization:				
Blood/plasma ratio:	-	-	-	
Plasma protein binding:	-	-	-	
Pharmacokinetics (e.g., Phase I) -				
<i>Healthy Volunteers-</i>				
single dose:	-	-	-	
multiple dose:				
<i>Patients-</i>				
single dose:	-	-	-	
multiple dose:	-	-	-	
Dose proportionality -				
fasting / non-fasting single dose:	-	-	-	
fasting / non-fasting multiple dose:	-	-	-	
Drug-drug interaction studies -				
In-vivo effects on primary drug:	-	-	-	
In-vivo effects of primary drug:	-	-	-	
In-vitro:				
Subpopulation studies -				
ethnicity:	-	-	-	
gender:	-	-	-	
pediatrics:	-	-	-	
geriatrics:				
renal impairment:	-	-	-	
hepatic impairment:	-	-	-	
PD:				
Phase 2:	-	-	-	
Phase 3:	-	-	-	
PK/PD:				
Phase 1 and/or 2, proof of concept:	-	-	-	
Phase 3 clinical trial:	-	-	-	
Population Analyses -				
Data rich:	-	-	-	
Data sparse:	-	-	-	
II. Biopharmaceutics				
Absolute bioavailability:	-	-	-	
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	-	-		
replicate design; single / multi dose:				
Food-drug interaction studies:	-			
Dissolution:	-	-	-	
(IVIVC):				
Bio-waiver request based on BCS	-	-	-	
BCS class				

III. Other CPB Studies				
Genotype/phenotype studies:	-	-	-	
Chronopharmacokinetics	-	-	-	
Pediatric development plan	-	-	-	
Literature References	X			~32 articles cited
Total Number of Studies		1		
Filability and QBR comments				
	"X" if yes	Comments		
Application filable?	X			
Comments sent to firm?	-			
QBR questions (key issues to be considered)	Given the formulation is similar. Is bio-waiver possible based on the in vitro testing of autoinjector?			
Other comments or information not included above	Application does not have PK studies.			
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

CC: NDA 22-377 HFD-850 (Electronic Entry), HFD-120, HFD-860 (Jagan Parepally, Ramana Uppoor, Mehul Mehta)

Appendix 1: Summary of Clinical Study

Table 12. Summary of Study Design and Key Objectives for the [Tradename] (Sumatriptan Succinate) Auto-Injector User Study – K644-07-3001

Study Identifier Phase Study Status Type of Report	Study Design	Key Objectives	Type of Subjects	Treatments Administered
K644-07-3001 Phase 3 Complete Final Clinical Study Report	Multicenter, open-label 2-week screening period Treatment of 1 migraine attack Follow-up evaluation within 72 hours	Primary Objective: <ul style="list-style-type: none"> • To assess the successful subcutaneous self-injection with a single 6 mg dose of sumatriptan succinate using the [Tradename] (sumatriptan succinate) Auto-Injector during a single migraine attack. Secondary Objectives: <ul style="list-style-type: none"> • To compare subcutaneous self-injection with sumatriptan using the [Tradename] (sumatriptan succinate) Auto-Injector with previously reported self-injection devices used to administer acute treatments for migraine and • To assess the tolerability of the [Tradename] (sumatriptan succinate) Auto-Injector when used to treat a migraine attack. 	Males and females ≥18 and ≤60 years of age, with a history of migraines (with or without aura) according to IHS criteria, with prior effective use of SC injectable SUM on ≥2 occasions within the previous 2 months	SUM 6 mg, administered SC using the [Tradename] Auto-Injector Although not supplied per protocol, a second dose of SUM (any formulation) was permitted 2 hours after dosing Rescue medications were permitted at the discretion of the Investigator

IHS = International Headache Society; SC = subcutaneous; SUM = sumatriptan.

Source: K644-07-3001 CSR

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/s/

Jagan Parepally
3/11/2009 09:52:19 AM
PHARMACOLOGIST

Ta-Chen Wu
3/11/2009 02:51:03 PM
BIOPHARMACEUTICS